## REMARKS

### Claim Amendements

Claims 1, 3, 5, 10-15, 18, 31-32, 40, 42, 95, 99, 147-148 and 150-151 are currently pending herein. Claims 1, 3, 5, 95, 99 and 148 have been amended herein. Claims 150-151 have been added herein. Claims 16 and 149 have been canceled herein. Claims 3, 5, 10-15, 18, 32, 40, 42, 95, 99, 147 and 150-151 have been withdrawn herein. Support for these amendments can be found throughout the specification and in the claims as previously filed. No new matter has been added.

### Rejoinder

Applicants believe that Claims 1, 31 and 148 are in condition for allowance and, therefore, respectfully request that withdrawn Claims 3, 5, 10-15, 18, 32, 40, 42, 95, 99, 147 and 150-151 be rejoined.

### Rejection of Claims 1, 31 and 148 Under requirements of 35 U.S.C. §103(a)

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Yu *et al.* (2000), in view of Kandimalla *et al.*, Liu et al. and Yu *et al.* (2002).

Applicants respectfully disagree. The instantly claimed invention is directed to an immunomer compound wherein at least one of the oligonucleotides of the immunomer is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG. For the reasons discussed below, the Office Action fails to make its *prima facie* case of obviousness in view of the cited art.

The Office Actions states that:

> It would have been obvious to substitute a first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a second bicyclic non-natural cytosine analogue having the structure shown in Figure 24 (Liu et al) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The

Moreover, the Office Action goes on to state that the

> selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA

However, the application of *KSR*, *Sinclair* and *In re Fout* in the instant rejection is unsupported and ignores the teachings and purpose of the instant invention.

**I. Reasonable expectation of success**

That the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. In other words, the mere fact that references can be combined or modified does not render the resultant combination obvious. One skilled in the art must have a reasonable expectation of success of reaching the instantly claimed invention.

In the instant case, the claims are directed to an immunomer wherein at least one of the oligonucleotides comprises an **immunostimulatory** dinucleotide having the structure RpG. Therefore, the overly simplistic view that the prior art could be combined such that the C of the CpG dinucleotide could be replace with the pyrrolo-dC described in Liu is insufficient. Rather, there must be a reasonable expectation of success that such a modification would still be immunostimulatory.

The cited art fails to provide such a reasonable expectation of success. Liu is completely silent regarding immunostimulatory oligonucleotides containing a CpG dinucleotide, or whether the dinucleotide can be modified, particularly with pyrrolo-dC, and still retain its immunostimulatory activity. Such a teaching or suggestion is not irrelevant, as modifying the CpG can negatively affect the ability to generate an immune response. In fact, as taught by Krieg (U.S. Patent 6,207,646)

> "Mitogenic ODN sequences uniformly became **nonstimulatory** if the CpG dinucleotide was mutated (Table 1; compare ODN 1 to 1a; 3D to 3Dc; 3M to 3Ma; and 4 to 4a) or if the cytosine of the CpG dinucleotide was replaced by 5-methylcytosine (Table 1; ODN 1b,2b,3Dd, and 3Mb). Partial methylation of CpG motifs caused a partial loss of stimulatory effect (compare 2a to 2c, Table 1). In contrast, methylation of other cytosines did not reduce ODN activity (ODN 1c, 2d, 3De and 3Mc). These data confirmed that a CpG motif is the **essential** element present in ODN that activate B cells." (emphasis added)

Furthermore, as stated by Applicants in response to previous Office Actions, which is incorporated herein by reference, Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside (referred to as "the first bicyclic non-natural cytosine" by the Office Action) showed **little or no immunostimulatory activity** (see

page 809, column 2, lines 22-24)(emphasis added). This was clarified by Dr. Kandimalla's declaration which stated that such a modification rendered the compound inactive. Thus, the Office Action fails to explain how one skilled in the art would have a reasonable expectation of success that a substitution with a "second bicyclic non-natural cytosine" would be immunostimulatory considering the first bicyclic non-natural cytosine was not functional.

Thus, based on the teachings of Krieg, and more importantly because of the lack of any teaching in Liu and the teaching away by Kandimalla, one skilled in the art would not have a reasonable expectation of success that the modification of the CpG dinucleotide as instantly claimed would yield a predictable result. As such, Claims 1, 31 and 148 are patentable over the cited art.

The rejection should be withdrawn for these reasons alone, however, Applicants will address the Office Action's second reason for rejecting the instant claims.

## II. Intended Use/Same purpose

In an attempt to support the rejection, and the relevance of Liu to the instantly claimed invention, the Office Action cites *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) ("The selection of a known material based on its suitability for its **intended use** supported a prima facie obviousness determination" (emphasis added)) and *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982) ("When substituting equivalents known in the prior art for the **same purpose**, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious" (emphasis added)).

The intended use of the instantly claimed invention is to generate an immune response; specifically, the instantly claimed immunomers are used to modify and/or enhance the immune response as compared to oligonucleotides having a wild-type CpG dinucleotide. The intended use of Liu is to use the intrinsically high fluorescence of pyrrolo-dC to gain "an understanding of the nature of the melted bubble which moves with the RNA polymerase active site" during transcription elongation.

There is nothing in the prior art to suggest that the intrinsically high fluorescence of pyrrolo-dC would make it suitable for replacing the C of the CpG dinucleotide for its use in generating an immune response. The Office Action attempts to overcome this deficiency by seeming concocting an arbitrary motivation to combine the references to reach the instantly

claimed invention. According to the Office Action, because Liu teaches that pyrrolo-dC is highly fluorescent and, therefore, useful for probing protein-nucleic acid interactions, one skilled in the art would have been motivated to modify the CpG dinucleotide with pyrollo-dC to study the structure-function relationships between CpG oligonucleotides and the protein receptor to which they bind. However, it is quite clear from the teachings of Liu that pyrrolo-dC would be completely unsuitable for studying this structure-function relationship.

Liu teaches the incorporation of pyrrolo-dC into duplex DNA and the formation of the elongation bubble which moves with the RNA polymerase active site. This elongation bubble is the site of local melting of the duplex DNA into single-stranded DNA that allows for the transcriptional enzyme to transcribe the template DNA strand into RNA.

Liu goes on to state that, like 2-aminopurine, pyrrolo-dC shows reduced fluorescence in duplex DNA relative to its fluorescence in single-stranded DNA and that this quenching of fluorescence is used to monitor local DNA melting. (see pg. 467, lines 1-5). Therefore, it is this melting of the duplex DNA into single-stranded DNA that increases the fluorescence of pyrrolo-dC and **not** any DNA-protein interaction.

As such, the fluorescent properties of pyrrolo-dC would be completely useless in the instant technological field as the instantly claimed compounds are single-stranded. There would be no change in the fluorescence levels of pyrrolo-dC regardless of whether the instantly claimed compound was interacting with the target receptor or not. Therefore, the use of pyrrolo-dC as taught by Liu would provide absolutely no useful information to one skilled in the art regarding the interaction between a CpG-containing oligonucleotide and its target protein receptor.

Thus, one skilled in the art simply would not consider pyrrolo-dC suitable for the intended purpose of the instant invention. As such, the Office Action fails to make its *prima facie* case. Reconsideration and withdrawal of the rejection are respectfully requested.

**Rejection of Claims 1, 31 and 148 Under requirements of 35 U.S.C. §103(a)**

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Yu *et al.* (2000), in view of Kandimalla *et al.*, Liu et al., Yu *et al.* (2002) and Hutcherson et al.

Applicants respectfully disagree. As stated above, Yu *et al.* (2000), in view of Kandimalla *et al.*, Liu et al. and Yu *et al.* (2002) fail to teach or suggest the instantly claimed

invention. Hutcherson et al. does not provide the teachings that the other references lack. Reconsideration and withdrawal of the rejection are respectfully requested.

**Provisional obviousness-type double patenting**

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/361,111; 10/865,245; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that, with regards to patent term, U.S. Application Nos. 10/361,111; 10/865,245; 11/153,054; and 11/174,002 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Once the instant claims have been allowed and these rejections have been withdrawn, Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications.

**CONCLUSION**

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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